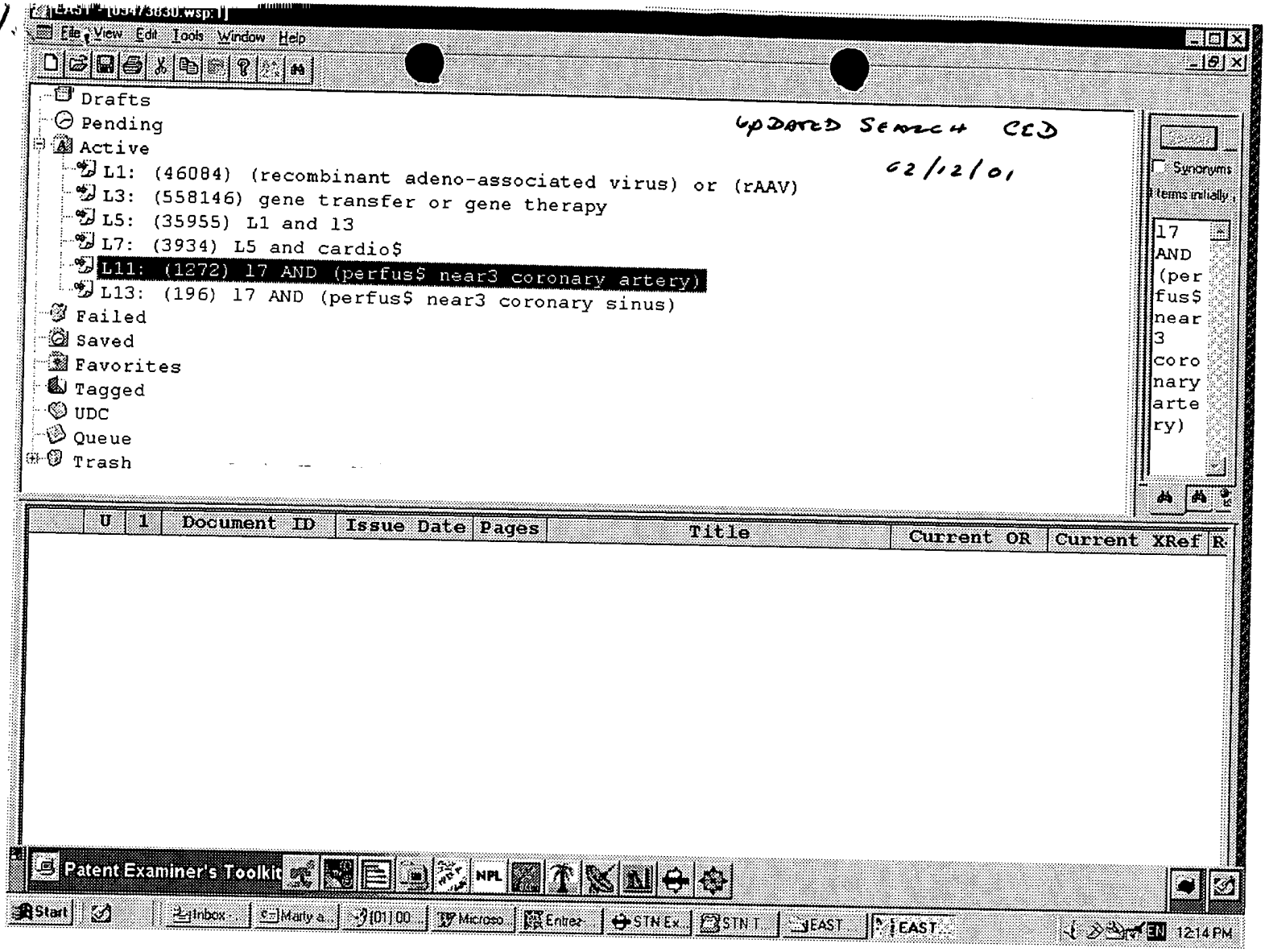
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L1: (46084) (recombinant adeno-associated virus) or (rAAV)
L3: (558146) gene transfer or gene therapy
L5: (35955) L1 and l3
L7: (3934) L5 and cardio$
L11: (1272) l7 AND (perfus$ near3 coronary artery)
L13: (196) l7 AND (perfus$ near3 coronary sinus)
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02/12/01

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                    Substances (PICCS) has been added to CHEMLIST
 NEWS  3  Oct 27    New Extraction Code PAX now available in Derwent
                    Files
 NEWS  4  Oct 27    SET ABBREVIATIONS and SET PLURALS extended in
                    Derwent World Patents Index files
 NEWS  5  Oct 27    Patent Assignee Code Dictionary now available
                    in Derwent Patent Files
 NEWS  6  Oct 27    Plasdoc Key Serials Dictionary and Echoing added to
                    Derwent Subscriber Files WPIDS and WPIX
 NEWS  7  Nov 29    Derwent announces further increase in updates for DWPI
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 NEWS  9  Dec  5    Trademarks on STN - New DEMAS and EUMAS Files
 NEWS 10  Dec 15    2001 STN Pricing
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                    biotechnology
 NEWS 12  Dec 17    Corrosion Abstracts on STN
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 NEWS 14  Dec 17    The CA Lexicon available in the CAPLUS and CA files
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FILE 'HOME' ENTERED AT 11:46:16 ON 12 FEB 2001

=> file dgene caplus biosis medline biotechds embase sciseearch

'SCISEEARCH' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
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specify a corrected file name or you can enter "IGNORE" to continue
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=> s ((rAAV) or (recombinant adeno associated vir?))

5 FILES SEARCHED...
L1 2108 ((RAAV) OR (RECOMBINANT ADENO ASSOCIATED VIR?))

=> L1 and (gene thaerapy or gene transfer)

L1 IS NOT A RECOGNIZED COMMAND
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For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s L1 and (gene thaerapy or gene transfer)

2 FILES SEARCHED...
L2 1003 L1 AND (GENE THAERAPY OR GENE TRANSFER)

=> s L1 and (gene therapy or gene transfer)

2 FILES SEARCHED...
6 FILES SEARCHED...
L3 1649 L1 AND (GENE THERAPY OR GENE TRANSFER)

=> L3 and cardio?

L3 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l3 and cardio?

L4 31 L3 AND CARDIO?

=> d his

FILE 'HOME' ENTERED AT 11:46:16 ON 12 FEB 2001

FILE 'DGENE, CAPLUS, BIOSIS, MEDLINE, BIOTECHDS, ASE, SCISEARCH'
ENTERED AT 11:47:28 ON 12 FEB 2001
L1 2108 S ((RAAV) OR (RECOMBINANT ADENO ASSOCIATED VIR?))
L2 1003 S L1 AND (GENE THAERAPY OR GENE TRANSFER)
L3 1649 S L1 AND (GENE THERAPY OR GENE TRANSFER)
L4 31 S L3 AND CARDIO?

=> dup rem l4

DUPLICATE IS NOT AVAILABLE IN 'DGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L4
L5 23 DUP REM L4 (8 DUPLICATES REMOVED)

=> d ibib abs l5 1-23

L5 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:456818 CAPLUS
DOCUMENT NUMBER: 133:53712
TITLE: Efficient and stable in vivo **gene transfer** to **cardiomyocytes** using **recombinant adeno-associated virus** vectors
INVENTOR(S): Leiden, Jeffrey M.; Svensson, Eric
PATENT ASSIGNEE(S): Arch Development Corp., USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038518	A1	20000706	WO 1999-US31093	19991228

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-113923 19981228

AB **Recombinant adeno-assocd. virus** (**rAAV**) vectors are used to transduce **cardiomyocytes** in vivo by infusing the **rAAV** into a coronary artery or coronary sinus. **RAAV** infection is not assocd. with detectable myocardial inflammation or myocyte necrosis. Thus, **rAAV** is a useful vector for the stable expression of therapeutic genes in the myocardium and can be used to deliver genes for inducing angiogenesis, inhibiting angiogenesis, stimulating cell proliferation, inhibiting cell proliferation and/or treating or ameliorating other **cardiovascular** conditions.

REFERENCE COUNT: 4
REFERENCE(S):
(1) Alexander; Clinical and Experimental Pharmacology and Physiology 1999, V26(9), P661 CAPLUS
(2) Gnatenko; Journal of Investigative Medicine 1997, V45(2), P87 MEDLINE
(3) Kaplitt; Annals of Thoracic Surgery 1996, V62(6), P1669 MEDLINE
(4) Svensson; Circulation 1999, V99(2), P201 MEDLINE

L5 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:839304 CAPLUS
DOCUMENT NUMBER: 133:345555
TITLE: A novel **recombinant adeno-associated virus** vector packaging system with HSV-1 amplicon providing helper functions
INVENTOR(S): Wu, Xiaobing; Wu, Zhijiang; Hou, Yunde
PATENT ASSIGNEE(S): National Major Laboratory of Virus & Gene Engineering, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 8 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1252441	A	20000510	CN 1999-119039	19990910

AB A novel packaging system for producing **recombinant adeno-assocd. virus** (**rAAV**) vector is described. Instead of the conventional method for **rAAV** prodn. by two-plasmid co-transfection followed by superinfection with adenovirus 5, a strategy of "one host cell line/one helper virus" is designed. An HSV-1 amplicon system expressing AAV-2 rep and cap genes from their native promoters was used to provide complete helper functions for **rAAV** replicating and packaging. This HSV-1 amplicon stock consisted of two kinds of infectious HSV-1 virions, a replicating-defective HSV-1 amplicon pseudovirus harboring multi-copies of AAV-2 rep and cap gene and a temp.-sensitive HSV-1 mutant strain ts-KOS. The process comprises prepg. **rAAV** packaging cell line; inserting AAV rep/cap gene into herpes simplex virus-I or(-II)at UL2 and/or UL44 gene to generate full functional helper virus; infecting **rAAV** packaging cells with HSV-1 helper virus for prepg. and screening for **rAAV** virus. The **rAAV** packaging cell contains AAV ITRs and therapeutic gene fragment. The **rAAV** packaging cell can be selected from BHk cell, KB cell, 293 cell, and HeLa cell. The **rAAV** vector contains antibiotic-resistance gene such as neo gene or hph gene. High-titer **rAAV** was generated with this new packaging system. This packaging system gives a simple and scaleable process for **rAAV** prodn. which can be used for gene delivery in **gene therapy**.

L5 ANSWER 3 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:312313 BIOSIS
DOCUMENT NUMBER: PREV200000312313
TITLE: Gene delivery to in situ veins: Differential effects of adenovirus and adeno-associated viral vectors.
AUTHOR(S): Eslami, Mohammad H.; Gangadharan, Sidhu P.; Sui, XinXin; Rhynhart, Kurt K.; Snyder, Richard O.; Conte, Michael S.
SOURCE: Journal of Vascular Surgery, (June, 2000) Vol. 31, No. 6, pp. 1149-1159. print.
ISSN: 0741-5214.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Purpose: **Gene transfer** offers the potential to modify vein graft biology at the time of surgical implantation. Efficiency of gene delivery, stability of expression, and host responses are critical parameters for candidate vectors. We compared the effects of intra-luminal exposure with adenovirus (AD) and adeno-associated virus (AAV) vectors on transgene expression and monocyte adhesion (MA) in treated vein segments.

Methods: Adult New Zealand white rabbits (N = 51) were anesthetized, and the jugular veins were cannulated bilaterally. Veins were gently distended with either vector (2.108 to 1.1010 infective particles/mL) or vehicle (control) for 30 minutes, after which venous flow was restored. AD and AAV vectors encoding for the marker genes beta-galactosidase (LacZ) and green fluorescent protein (GFP) were used. Vessels were explanted 2 to 40 days postinfection for analysis of gene expression (X-gal staining, reverse transcriptase-polymerase chain reaction), MA, and immunohistochemistry. Ex vivo adhesion assays used 51Cr-labeled THP-1 cells. Statistical significance was tested by using analysis of variance with a P value less than .05. Results: All animals survived, and all treated veins were patent at sacrifice. Intraluminal exposure to AD at a titer of 1.109 resulted in near complete transduction of the endothelium at 2 days, with no detectable expression by day 14. At an equal titer of infectious particles, transgene expression was markedly less for AAV at 2 to 7 days, but improved at 2 weeks and persisted to 40 days. MA was significantly increased 2 days after AD exposure (2.7-fold vs control, *P < .002); AAV treatment had no discernible effect on MA. Conclusion: AD-mediated **gene transfer** to vein segments resulted in robust, transient gene expression that disappeared after 2 weeks. In comparison, AAV-mediated gene delivery was less efficient, but resulted in delayed onset, persistent expression beyond 30 days. AD exposure induced an early increase in MA to the vein surface that was not seen with AAV treatment. Current generations of both AD and AAV vectors have significant, albeit different, limitations for vascular **gene therapy**.

L5 ANSWER 4 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:523433 BIOSIS
DOCUMENT NUMBER: PREV200000523433
TITLE: **Gene therapy** for hypertension: **Recombinant adeno-associated virus** vector delivery of angiotensin type 1 receptor antisense in hypertensive double transgenic mice.
AUTHOR(S): Phillips, M. Ian (1); Kimura, Birgitta (1); Zhang, Y. Clare (1); Gelband, Craig H. (1); Sigmund, Curt D.; Mohuczy, Dagmara
CORPORATE SOURCE: (1) Univ of Florida, Gainesville, FL USA
SOURCE: Hypertension (Baltimore), (October, 2000) Vol. 36, No. 4, pp. 730. print.
Meeting Info.: 54th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research Washington, DC, USA November 24-27, 2000
ISSN: 0194-911X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 5 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:523428 BIOSIS
DOCUMENT NUMBER: PREV200000523428
TITLE: Attenuation of hypertension and heart hypertrophy by **recombinant adeno-associated virus** delivering angiotensinogen antisense (**rAAV**-AGT-AS.
AUTHOR(S): Kimura, Birgitta (1); Mohuczy, Dagmara (1); Tang, Xiaoping (1); Phillips, M. Ian (1)
CORPORATE SOURCE: (1) Univ of Florida, Gainesville, FL USA
SOURCE: Hypertension (Baltimore), (October, 2000) Vol. 36, No. 4, pp. 729. print.
Meeting Info.: 54th Annual Fall Conference and Scientific

Sessions of the Council for High Blood Pressure Research
Washington, DC, USA November 24-27, 2000
ISSN: 0194-911X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 6 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:488112 BIOSIS
DOCUMENT NUMBER: PREV200000488233
TITLE: **Gene therapy** vectors based on adeno-associated virus: Characteristics and applications to acquired and inherited diseases (Review.
AUTHOR(S): Athanasopoulos, Takis; Fabb, Stewart; Dickson, George (1)
CORPORATE SOURCE: (1) University Chair of Molecular Cell Biology, School of Biological Sciences, Division of Biochemistry, Royal Holloway College, University of London, Egham Hill, Egham, Surrey, TW20 0EX UK
SOURCE: International Journal of Molecular Medicine, (October, 2000) Vol. 6, No. 4, pp. 363-375. print.
ISSN: 1107-3756.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Adeno-associated virus (AAV), a defective parvovirus, was discovered more than 30 years ago. Interest in this virus for human **gene therapy** applications focuses on its non-pathogenicity, broad tropism and infectivity, site-specific integration and long-term persistence. The field of **rAAV** research has considerably advanced: titers of 1014 p/ml have been achieved, plasmid systems devised to produce helper-free viruses, chimaeric vectors combining properties of **rAAV** ITRs and large sequence capacity from Ad/HS vectors in parallel with the revolutionary intron strategy based on heterodimerisation of the forming concatamers have expanded the vector capacity. Muscle cells and neurons (post-mitotic cells) are amongst the most efficient targets of **rAAV** delivery and AAV receptors and co-receptors have been identified. This review will describe advances in the field of **rAAV** technology that overcome certain limitations of the vector as a gene delivery system and overview applications involving these recombinant vectors for the treatment of acquired and inherited diseases.

L5 ANSWER 7 OF 23 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:872601 SCISEARCH
THE GENUINE ARTICLE: 351BR
TITLE: Morphological and physiological rescue of dilated **cardiomyopathy** (DCM) by **rAAV** vector-mediated **gene transfer** in vivo
AUTHOR: Kawada T (Reprint); Nakazawa M; Sakamoto A; Urabe M; Wang Y; Ozawa K; ToyoOka T
CORPORATE SOURCE: NIIGATA UNIV, HOSP MED, DIV PHARM, NIIGATA, JAPAN; NIIGATA UNIV, SCH MED, DEPT PHARMACOL, NIIGATA 951, JAPAN; NATL CARDIOVASC RES CTR, DIV BIOTECHNOL, OSAKA, JAPAN; JICHI MED SCH, DIV GENET THERAPEUT, TOCHIGI, JAPAN; UNIV TOKYO, DEPT INTERNAL MED, TOKYO, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: EUROPEAN HEART JOURNAL, (AUG-SEP 2000) Vol. 21, Supp. [S], pp. 132-132.
Publisher: W B SAUNDERS CO LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 0195-668X.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: CLIN

LANGUAGE: English
REFERENCE COUNT: 0

L5 ANSWER 8 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:35379 BIOSIS
DOCUMENT NUMBER: PREV200100035379
TITLE: Rescue of DCM by **gene therapy**: A novel and general scheme for advancing heart failure and its protection.
AUTHOR(S): Toyo-Oka, T. (1); Kawada, T.; Nakazawa, M.; Sakamoto, A.; Urabe, M.; Masui, F.; Yoshida, H.; Nakauchi, S.; Xi, H.; Shin, W. S.; Sato, H.; Monahan, J.; Takeo, S.; Ozawa, K.
CORPORATE SOURCE: (1) Dept. Cardiovasc. Med., Univ. Tokyo, Tokyo Japan
SOURCE: Journal of Molecular and Cellular Cardiology, (November, 2000) Vol. 32, No. 11, pp. A88. print.
Meeting Info.: XVII Annual Meeting of the International Society for Heart Research, Japanese Section Osaka, Japan December 06-08, 2000 International Society for Heart Research
. ISSN: 0022-2828.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 9 OF 23 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:53243 SCISEARCH
THE GENUINE ARTICLE: 367QE
TITLE: Dilated **cardiomyopathy** (DCM) is rescued by **recombinant adeno-associated virus** (**rAAV**)-mediated somatic **gene therapy**
AUTHOR: Toyo-Oka T (Reprint); Kawada T; Nakazawa M; Sakamoto A; Urabe M; Wang Y; Shin W S; Sato H; Monahan J; Ozawa K
CORPORATE SOURCE: Univ Tokyo, Tokyo, Japan; Niigata Univ, Hosp Med, Div Pharma, Niigata, Japan; Niigata Univ, Niigata, Japan; NCVRC, Biotech Div, Osaka, Japan; Jichi Med Sch, Tochigi, Japan; Univ Tokyo, Tokyo, Japan; Avigen Inc, Alameda, CA USA
COUNTRY OF AUTHOR: Japan; USA
SOURCE: CIRCULATION, (31 OCT 2000) Vol. 102, No. 18, Supp. [S], pp. 11-11. MA 42.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0009-7322.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0

L5 ANSWER 10 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:481338 BIOSIS
DOCUMENT NUMBER: PREV200000481338
TITLE: Morphological and physiological rescue of dilated **cardiomyopathy** (DCM) by **rAAV** vector-mediated **gene transfer** in vivo.
AUTHOR(S): Kawada, T. (1); Nakazawa, M.; Sakamoto, A.; Urabe, M.; Wang, Y.; Ozawa, K.; Toyo-Oka, T.
CORPORATE SOURCE: (1) Div. of Pharmacy, Niigata Univ. Medical Hospital, Niigata Univ. School of Medicine, Niigata Japan
SOURCE: European Heart Journal, (August September, 2000) Vol. 21, No. Abstract Supplement, pp. 3. print.
Meeting Info.: XXII Congress of the European Society of Cardiology Amsterdam, Netherlands August 26-30, 2000 European Society of Cardiology
. ISSN: 0195-668X.
DOCUMENT TYPE: Conference
LANGUAGE: English

SUMMARY LANGUAGE: English

L5 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:68588 BIOSIS
DOCUMENT NUMBER: PREV200100068588
TITLE: Dilated **cardiomyopathy** (DCM) is rescued by **recombinant adeno-associated virus** (**rAAV**)-mediated somatic **gene therapy**.
AUTHOR(S): Toyo-Oka, Teruhiko (1); Kawada, Tomie; Nakazawa, Mikio; Sakamoto, Aiji; Urabe, Masashi; Wang, Yue; Shin, Wee Soo; Sato, Hiroshi; Monahan, John; Ozawa, Keiya
CORPORATE SOURCE: (1) Univ of Tokyo, Tokyo Japan
SOURCE: Circulation, (October 31, 2000) Vol. 102, No. 18 Supplement, pp. II.11. print.
Meeting Info.: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:635437 CAPLUS
DOCUMENT NUMBER: 131:253345
TITLE: Adeno-associated virus vectors for **gene therapy** of muscle disease
INVENTOR(S): Podsakoff, Gregory M.; Kessler, Paul D.; Byrne, Barry J.; Kurtzman, Gary J.
PATENT ASSIGNEE(S): Avigen, Inc., USA; Johns Hopkins University
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 588,355.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5962313	A	19991005	US 1997-784757	19970116
US 5858351	A	19990112	US 1996-588355	19960118
WO 9726337	A1	19970724	WO 1997-US895	19970117
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2243261	AA	19970724	CA 1997-2243261	19970117
EP 874904	A1	19981104	EP 1997-904823	19970117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:
US 1996-588355 19960118
US 1997-784757 19970116
WO 1997-US895 19970117

AB The use of **recombinant adeno-assocd. virus** (AAV) virions for delivery of therapeutic genes to muscle is disclosed. The invention allows for the direct, in vivo injection of recombinant AAV virions into muscle tissue, as well as for the in vitro transduction of muscle cells that can subsequently be introduced into a subject for treatment. The invention provides for sustained, high-level expression of the delivered gene and for in vivo secretion of the therapeutic protein from transduced muscle cells such that systemic delivery is achieved. Adeno-assocd. virus can transform myocytes and **cardiomyocytes** with a lacZ reporter gene in vitro. Transformation of mouse myotubes and myoblasts with a virus carrying the human erythropoietin gene led to the synthesis of the protein by transformed cells for 6-8 wk. I.m. injection was mor effective at transformation of muscle cells and tissues than was i.v. injection. Use of an AAV vector to

deliver an acid .alpha.-glucosidase gene that could be used for therapy of

cardiomyopathy a[redacted]cd. with glycogen storage dise[redacted]s is described. Mice inoculated i.m. with the virus produced elevated levels of the enzyme for 10 wk.

REFERENCE COUNT: 30
REFERENCE(S):
(2) Acsadi; Hum Mol Genetics 1994, V3, P579 CAPLUS
(3) Acsadi; Nature 1991, V352, P815 CAPLUS
(4) Anon; WO 9413788 1994 CAPLUS
(5) Anon; WO 9513376 1995 CAPLUS
(6) Anon; WO 9520671 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 1999:257740 CAPLUS
DOCUMENT NUMBER: 131:53931
TITLE: Stable restoration of the sarcoglycan complex in dystrophic muscle perfused with histamine and a **recombinant adeno-associated viral** vector
AUTHOR(S): Greelish, James P.; Su, Leonard T.; Lankford, Edward B.; Burkman, James M.; Chen, Haiyan; Konig, Stephane K.; Mercier, Isabelle M.; Desjardins, Philippe R.; Mitchell, Marilyn A.; Zheng, Xiang Guang; Leferovich, John; Ping, Guang Gao; Balice-Gordon, Rita J.; Wilson, James M.; Stedman, Hansell H.
CORPORATE SOURCE: Departments of Surgery', Medicine, Neuroscience3 and Molecular and Celldlar Engineerirng and Institute for Human Gene Therapy, University of Pennsylvania Health System, Philadelphia, PA, 19104, USA
SOURCE: Nat. Med. (N. Y.) (1999), 5(4), 439-443
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Limb-girdle muscular dystrophies 2C-F represent a family of autosomal recessive diseases caused by defects in sarcoglycan genes. The **cardiomyopathic** hamster is a naturally occurring model for limb-girdle muscular dystrophy caused by a primary deficiency in .delta.-sarcoglycan. We show here that acute sarcolemmal disruption occurs in this animal model during forceful muscle contraction. A **recombinant adeno-assocd. virus** vector encoding human .delta.-sarcoglycan conferred efficient and stable genetic reconstitution in the adult **cardiomyopathic** hamster when injected directly into muscle. A quant. assay demonstrated that vector-transduced muscle fibers are stably protected from sarcolemmal disruption; there was no assocd. inflammation or immunol. response to the vector-encoded protein. Efficient gene transduction with rescue of the sarcoglycan complex in muscle fibers of the distal hindlimb was also obtained after infusion of **recombinant adeno-assocd. virus** into the femoral artery in conjunction with histamine-induced endothelial permeabilization. This study provides a strong rationale for the develop of **gene therapy** for limb-girdle muscular dystrophy.
REFERENCE COUNT: 21
REFERENCE(S):
(3) Cox, G; Nature 1993, V364, P725 CAPLUS
(4) Cox, G; Nature Genet 1994, V8, P333 CAPLUS
(5) DeMatteo, R; J Virol 1997, V71, P5330 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:123147 BIOSIS

DOCUMENT NUMBER: PREV199900123147
TITLE: Antisense inhibition of AT1 receptor in vascular smooth muscle cells using adeno-associated virus-based vector.
AUTHOR(S): Moravec, Dagmara; Gelband, Craig H.; Phillips, M. Ian (1)
CORPORATE SOURCE: (1) Dep. Physiol., Coll. Med., Univ. Fla., Box 100274, Gainesville, FL 32610 USA
SOURCE: Hypertension (Baltimore), (Jan., 1999) Vol. 33, No. 1 PART 2, pp. 354-359.
ISSN: 0194-911X.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Vascular smooth muscle cells (VSMCs) are the main peripheral target for vasoconstriction and growth-promoting activity of angiotensin II (Ang II), acting through angiotensin type I receptors (AT1-R). Current antihypertension treatments include daily reductions in the effects of Ang II. To decrease an effect of Ang II in a prolonged fashion, we have developed an adeno-associated virus (AAV) vector with antisense DNA for AT1-R. AAV has many advantages over other viral vectors. AAV is nonpathogenic, does not stimulate inflammation or immune reaction and enters nondividing cells, and provides stable long-term gene expression. To test AAV in VSMCs, we constructed and tested plasmid AAV (pAAV) and recombinant AAV (**rAAV**) with AT1-R antisense DNA. **rAAV** was constructed with a cassette containing a cytomegalovirus promoter and the cDNA for the AT1-R inserted in the antisense direction. The cassette was packaged into the virion. Transfection of VSMCs with the pAAV antisense to AT1-R produced a significant reduction in the amount of AT1-R ($P<0.01$). Transduction of VSMCs with the **rAAV**-AT1-R-AS at MOI of 5 also showed significant reduction of AT1-R and long-lasting expression of the transgene for at least 8 weeks. The reduction of AT1-R number in VSMCs was concomitant with a decrease in the Ang 11-stimulated increase of intracellular calcium. The results show that AAV vector delivers AT1-R antisense to inhibit AT1-R in VSMCs. For the purpose of **gene therapy** for hypertension, it is necessary to demonstrate the effectiveness of a vector system in VSMCs. This study provides support for the potential use of AAV AT1-R antisense in VSMCs.

L5 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 1999:86561 BIOSIS
DOCUMENT NUMBER: PREV199900086561
TITLE: Efficient and stable transduction of **cardiomyocytes** after intramyocardial injection or intracoronary perfusion with **recombinant adeno-associated virus** vectors.
AUTHOR(S): Svensson, Eric C.; Marshall, Deborah J.; Woodard, Karen; Lin, Hua; Jiang, Fang; Chu, Lein; Leiden, Jeffrey M. (1)
CORPORATE SOURCE: (1) Univ. Chicago, Room B608 MC 6080, 5841 S. Maryland Ave., Chicago, IL 60637 USA
SOURCE: Circulation, (Jan. 19, 1999) Vol. 99, No. 2, pp. 201-205.
ISSN: 0009-7322.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Background-The delivery of recombinant genes to **cardiomyocytes** holds promise for the treatment of a variety of **cardiovascular** diseases. Previous **gene transfer** approaches that used direct injection of plasmid DNA or replication-defective adenovirus vectors have been limited by low transduction frequencies and transient transgene expression due to immune responses, respectively. In this report, we have tested the feasibility of using intramyocardial injection or intracoronary infusions of **recombinant adeno-associated virus** (**rAAV**) vectors to program transgene expression in murine **cardiomyocytes** in vivo. Methods

and Results-We constructed an **rAAV** containing the LacZ gene under the transcriptional control of the cytomegalovirus (CMV) promoter (AAVCMV-LacZ). When injected 1 X 108 infectious units (IU) of this virus into the left ventricular myocardium of adult CD-1 mice. Control hearts were injected with the AdCMV-LacZ adenovirus vector. Hearts harvested 2, 4, and 8 weeks after AAVCMV-LacZ injection demonstrated stable beta-galactosidase (beta-gal) expression in large numbers of **cardiomyocytes** without evidence of myocardial inflammation or myocyte necrosis. In contrast, the AdCMV-LacZ-injected hearts displayed transient beta-gal expression, which was undetectable by 4 weeks after injection. Explanted C57BL/6 mouse hearts were also perfused via the coronary arteries with 1.5 X 109 IU of AAVCMV-LacZ and assayed 2, 4, and 8 weeks later for beta-gal expression. beta-Gal expression was detected in <1% of **cardiomyocytes** at 2 weeks after perfusion but was detected in up to 50% of **cardiomyocytes** 4 to 8 weeks after perfusion. Conclusions-Direct intramyocardial injection or coronary artery perfusion with **rAAV** vectors can be used to program stable transgene expression in **cardiomyocytes** in vivo. **rAAV** appears to represent a useful vector for the delivery of therapeutic genes to the myocardium.

L5 ANSWER 16 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:524127 BIOSIS
DOCUMENT NUMBER: PREV199800524127
TITLE: **Recombinant adeno-associated virus**-mediated **gene transfer** in the in vivo rabbit myocardium.
AUTHOR(S): Wright, M. J. (1); De Alwis, M.; Latchman, D. S.; Thrasher, A. J.; Marber, M. S. (1)
CORPORATE SOURCE: (1) Dep. Cardiol., Rayne Inst., United Med. Dent. Sch., St. Thomas' Hosp., London UK
SOURCE: European Heart Journal, (Aug., 1998) Vol. 19, No. ABST. SUPPL., pp. 478.
Meeting Info.: XXth Congress of the European Society of Cardiology Vienna, Austria August 22-26, 1998 European Society of Cardiology
. ISSN: 0195-668X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L5 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:21340 CAPLUS
DOCUMENT NUMBER: 130:217932
TITLE: **Gene therapy** for hypertension: antisense inhibition with adeno-associated viral vector delivery targeting angiotensin II type 1-receptor messenger ribonucleic acid
AUTHOR(S): Phillips, M. Ian
CORPORATE SOURCE: University of Florida College of Medicine, Gainesville, FL, 32610-0274, USA
SOURCE: Am. J. Cardiol. (1998), 82(10A), 60S-62S
CODEN: AJCDAG; ISSN: 0002-9149
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our findings suggest that prolonged redns. in blood pressure can be achieved with single doses of AAV vectors delivering antisense oligodeoxynucleotides to inhibit AT1 receptors. The findings employing antisense oligodeoxynucleotides to AT1 in spontaneously hypertensive rats recently have been extended to the 2-kidney/1-clip and cold-induced animal

models of hypertension. We have developed **rAAV**-AS vectors to deliver antisense oligodeoxynucleotides targeted to angiotensinogen and the angiotensin-converting enzyme gene. One object of further study is to identify efficient and powerful promoters to be included in DNA vectors. The results of our studies to date encourage a vision of a i-shot **gene therapy** controlling hypertension for months without side effects and thereby protecting patients from **cardiovascular** risks assocd. with high blood pressure.

REFERENCE COUNT: 8
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 23 BIOTECHDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-10823 BIOTECHDS
TITLE: Delivering gene to muscle cell or tissue using **recombinant adeno-associated virion**; for use in **gene therapy** and as recombinant vaccine
AUTHOR: Podsakoff G M; Kessler P D; Byrne B J; Kurtzman G J
PATENT ASSIGNEE: Avigen; Univ.Johns-Hopkins
LOCATION: Alameda, CA, USA; Baltimore, MD, USA.
PATENT INFO: WO 9726337 24 Jul 1997
APPLICATION INFO: WO 1997-US895 17 Jan 1997
PRIORITY INFO: US 1997-784757 16 Jan 1997; US 1996-588355 18 Jan 1996
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1997-385340 [35]
AN 1997-10823 BIOTECHDS
AB A new composition useful for delivering a selected gene to a muscle cell (preferably a skeletal myoblast, skeletal myocyte or **cardiomyocyte**) or tissue (e.g. derived from skeletal, smooth or cardiac muscle) contains a **recombinant adeno-associated virus** (AAV) virion containing the target gene linked to control elements. The gene preferably encodes a therapeutic protein, especially acid alpha-glucosidase (EC-3.2.1.20). The control elements consist of an inducible muscle-specific promoter sequence. Also claimed is a muscle cell or tissue transduced in vitro with the recombinant AAV virion. The virions may be used for treating type II glycogen storage disease. The target gene may also encode erythropoietin and other proteins capable of treating endocrine, metabolic, hematological and **cardiovascular** diseases including AIDS, cancer and diabetes. The virions are non-pathogenic and may be used for the delivery of antigens for immunization. Cells transduced provide sustained, high-level expression of the target gene, and the protein is secreted to provide systemic delivery. (76pp)

L5 ANSWER 19 OF 23 BIOTECHDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-00955 BIOTECHDS
TITLE: **Gene transfer** into vascular cells using adeno-associated virus (AAV) vectors; **recombinant adeno-associated virus** vector-mediated beta-galactosidase reporter **gene transfer** to rat vascular smooth muscle cell and thoracic aorta for **gene therapy**
AUTHOR: Maeda Y; Ikeda U; Ogasawara Y; Urabe M; Takizawa T; Saito T; Colosi P; Kurtzman G; Shimada K; *Ozawa K
CORPORATE SOURCE: Jichi-Med.Sch.; Inst.Hematol.Tochigi; Avigen

LOCATION: Department of Molecular Biology, Institute of Hematology, Jichi Medical School, Minamikawachi-machi, Tochigi 329-04, Jap[redacted]
Email: kozawa@jichi.ac.jp
SOURCE: Cardiovasc.Res.; (1997) 35, 3, 514-21
CODEN: CVREAU
ISSN: 0008-6363
DOCUMENT TYPE: Journal
LANGUAGE: English
AN 1998-00955 BIOTECHDS
AB Beta-galactosidase (EC-3.2.1.23) reporter **gene transfer** into rat vascular smooth muscle cells (VSMCs) and rat thoracic aortas was investigated using **recombinant adeno-associated virus** vectors. VSMCs were transduced at a moi of 500,000 to 10 million. Beta-galactosidase expression in VSMCs was evaluated by X-Gal staining and an ELISA method. Excised rat aortas were incubated with medium containing the vector. Expression of beta-galactosidase in the aortic segments was evaluated by X-Gal staining. With increasing moi, up to 50% of cultured VSMCs were positive by X-Gal staining and the enzyme expression increased up to 15 ng/mg protein. The expression gradually decreased during the culture but was detectable for at least 1 mth. In the ex vivo study, vectors transduced endothelial and adventitial cells in rat aortic segments, while no expression was seen in medial VSMCs. Thus, adeno-associated virus vectors can efficiently transduce rat VSMCs in vitro. Results suggest that such vectors may be used for **cardiovascular** disease **gene therapy**. (34 ref)

L5 ANSWER 20 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:200716 BIOSIS
DOCUMENT NUMBER: PREV199799499919
TITLE: Adeno-associated virus vectors for vascular gene delivery.
AUTHOR(S): Lynch, Carmel M. (1); Hara, Paul S.; Leonard, Jill C.; Williams, J. Koudy; Dean, Richard H.; Geary, Randolph L.
CORPORATE SOURCE: (1) Targeted Genetics Corp., 1100 Olive Way, Suite 100, Seattle, WA 98101 USA
SOURCE: Circulation Research, (1997) Vol. 80, No. 4, pp. 497-505. ISSN: 0009-7330.
DOCUMENT TYPE: Article
LANGUAGE: English
AB A variety of delivery systems have been used to genetically modify vascular endothelial cells and smooth muscle cells (SMCs), but currently available systems suffer from either inefficient in vivo **gene transfer**, transient episomal vector expression, or significant immune responses and inflammation. In the present study, we evaluated an alternate vector system, **recombinant adeno-associated virus** (**rAAV**) for transduction of vascular cells in culture and in vivo. Primary cultures of rabbit, monkey, and human SMCs; macaque and human microvascular endothelial cells; and human umbilical vein endothelial cells were efficiently transduced at a dose of 100 to 1000 DNase-resistant particles per cell. **rAAV**-mediated transduction of the vasculature in vivo was observed after intraluminal gene delivery or after intra-adventitial injection in carotid arteries of atherosclerotic cynomolgus monkeys. Whether vector delivery was intraluminal or adventitial, transduction was observed in the adventitia, particularly within microvessels (vasa vasorum) but not in cells of the intima or media. Transduction of adventitial microvessels was enhanced by balloon injury 4 days before **gene transfer**. This was particularly true for adventitial delivery. We have previously

shown that adventitial cell proliferation increases significantly 4 days after balloon injury (45%) in this animal model. Together, these data suggest that cell proliferation may enhance AAV transduction in vivo in the vasculature. AAV vectors exhibited a tropism in vivo for the microvascular endothelium at the doses used in the present study, which may provide the opportunity for targeting gene delivery. In summary, we have demonstrated the utility of **rAAV** vectors for ex vivo vascular cell gene delivery and present an initial experience with **rAAV** for in vivo vascular gene delivery. This alternate vector system may overcome some of the limitations hampering the development of **gene therapy** for vascular disorders.

L5 ANSWER 21 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:127708 BIOSIS
DOCUMENT NUMBER: PREV199799419521
TITLE: Prolonged reduction of high blood pressure with an in vivo, nonpathogenic, adeno-associated viral vector delivery of AT-1-R mRNA antisense.
AUTHOR(S): Phillips, M. Ian (1); Mohuczy-Dominiak, Dagmara; Coffey, Mark; Galli, Sara M.; Kimura, Birgitta; Wu, Ping; Zelles, Tibor
CORPORATE SOURCE: (1) Dep. Physiol., Coll. Med., Univ. Florida, Gainesville, FL 32610 USA
SOURCE: Hypertension (Dallas), (1997) Vol. 29, No. 1 PART 2, pp. 374-380.
ISSN: 0194-911X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB To produce a prolonged decrease in blood pressure, we have developed a nonpathogenic adeno-associated viral vector (AAV) with the antisense DNA for AT-1-R. AAV has many advantages over other viral vectors. AAV does not stimulate inflammation or immune reaction. AAV enters nondividing cells and does not replicate. Therefore, it is an appropriate choice for **gene therapy**. Recombinant AAV was prepared with a cassette containing a cytomegalovirus promoter and the cDNA for the AT, receptor inserted in the antisense direction. The cassette was packaged in the virion. Stable transfection of NG108-15 cells with the pAAV-AS (plasmid AAV) antisense to AT-1-R produced a significant reduction in AT-1 receptors. A single injection of the **rAAV**-AS (viral vector) was made in adult spontaneously hypertensive rats, either directly in the hypothalamus (1 mu-L) or in the lateral ventricles (5 mu-L). The result shows that there is a significant decrease of blood pressure (apprxeq 23 +- 2 mm Hg) for up to 9 weeks after injection. Control injections of mock vector produced no change in blood pressure during the same time period in age-matched controls. In young spontaneously hypertensive rats (3 weeks), a single intracardiac injection of recombinant **rAAV**-AS reduced blood pressure and slowed the development of hypertension compared with controls (P lt .01). The results suggest that a prolonged reduction in high blood pressure can be achieved with AAV vectors delivering antisense to inhibit AT-1 receptors with a single administration.

L5 ANSWER 22 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:179938 BIOSIS
DOCUMENT NUMBER: PREV199799471651
TITLE: In vivo **gene transfer** into rat arterial walls with novel adeno-associated virus vectors.
AUTHOR(S): Arnold, Thomas E. (1); Gnatenko, Dmitri; Bahou, Wadie F.
CORPORATE SOURCE: (1) Dep. Surg., Health Sci. Cent., T-19, 020, SUNY at Stony Brook, Stony Brook, NY 11794-8191 USA
SOURCE: Journal of Vascular Surgery, (1997) Vol. 25, No. 2, pp.

347-355.
ISSN: 0741-5214.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Purpose. We studied the ability of **recombinant adeno-associated virus** (**rAAV**) vectors to achieve **gene transfer** in vivo to intact rat carotid arteries. Methods. Isolated segments of uninjured rat carotid arteries were incubated with (1) **rAAV** vectors that expressed a beta-galactosidase gene, (2) a related vector with no promoter, or (3) a normal saline solution. **Gene transfer** was evaluated with in situ polymerase chain reaction (PCR). Transgene expression was assessed at intervals that ranged from 24 hours to 2 months by measurement of beta-galactosidase activity and protein mass in tissue extracts with fluorometric and enzyme-linked immunosorbent assays, respectively. Dose dependence of expression was determined for virus concentrations that ranged from 5 times 10-4 to 5 times 10-5 infectious units (iu)/ml. Results. Light microscopic analysis of in situ PCR-stained histologic sections of transduced vessel walls showed approximately 90% of intimal and medial cell nuclei contained the beta-galactosidase gene, compared with none in control arteries. In vivo beta-galactosidase expression was (1) highest 24 hours after **gene transfer**, (2) elevated for 1 month, and (3) dose responsive. Conclusions. **rAAV** vectors can mediate focal **gene transfer** into the intact rat carotid artery with detectable levels of transgene expression for 1 month and are potentially useful agents for in vivo **gene transfer** into intact arteries.

L5 ANSWER 23 OF 23 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:127695 BIOSIS
DOCUMENT NUMBER: PREV199799419508
TITLE: Antisense inhibition and adeno-associated viral vector delivery for reducing hypertension.
AUTHOR(S): Phillips, M. Ian
CORPORATE SOURCE: Dep. Physiol., Coll. Med, Box 100274, Univ. Florida, Gainesville, FL 32610-0274 USA
SOURCE: Hypertension (Dallas), (1997) Vol. 29, No. 1 PART 2, pp. 177-187.
ISSN: 0194-911X.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Antisense oligodeoxynucleotides have been designed to inhibit the production of specific proteins. In models of hypertension, we have targeted the renin-angiotensin system at the level of synthesis (angiotensinogen) and the receptor (AT-1 receptor). The design of antisense oligonucleotides requires choosing a site to inhibit mRNA processing or translation. The strategy we use is to make three oligonucleotides of antisense sequences, upstream and downstream from the AUG site and over the AUG site. The oligonucleotides are tested in a screening test. Antisense oligonucleotides to AT-1-receptor mRNA and to angiotensinogen mRNA reduce blood pressure in spontaneously hypertensive rats when injected into the brain. They significantly reduce the concentration of the appropriate protein. The oligonucleotides are also effective when administered systemically. The decrease in blood pressure with antisense oligonucleotides delivered in blood or brain lasts 3 to 7 days. To prolong the action, direct injection of naked DNA and injection of DNA in liposome carriers have been tested. Viral vectors have been developed to deliver antisense DNA. The viral vectors available include retroviruses and adenovirus, but the adeno-associated virus (AAV) vector is the vector of choice for ultimate use in **gene therapy**. It offers safety because it is nonpathogenic, has longevity because it integrates into the genome, and has sufficient carrying capacity to carry up to 4.5 kb antisense or gene in a recombinant AAV. Using **rAAV**-antisense to AT-1 mRNA, there is efficient transfection into cells and an

inhibition of AT-1 receptor number. In in vivo tests, **rAAV**-AS AT-1-receptor when injected into the brains of SHR reduces blood pressure for more than 2 months. In young rats (3 weeks old) **rAAV**-AS AT-1-receptor decreases blood pressure and slows the development of hypertension. While further experiments need to be done on dose-response relationships and on the cellular mechanisms of these effects, the results show the feasibility of AAV as a vector for antisense inhibition, which may ultimately be used in **gene therapy** for hypertension.